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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/825,687	04/16/2004	Lucile Miquerol	37991-0013	8859

26633 7590 03/29/2007

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EXAMINER	
NOBLE, MARCIA STEPHENS	
ART UNIT	PAPER NUMBER
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/29/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/825,687	MIQUEROL ET AL.	
	Examiner	Art Unit	
	Marcia S. Noble	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *10-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 January 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 1-15 are pending. Preliminary amendment of claims, filed 1/16/2007 is acknowledged.

Election/Restrictions

2. Applicant's election without traverse of Group I, claims 1-9, drawn to a transgenic mouse that has integrated a reporter gene in the locus of the Cx40 gene, in the reply filed on 1/16/2007 is acknowledged.

Claims 10-15 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected subject mater, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 1/16/2007.

Claims 1-9 are under consideration.

Information Disclosure Statement

3. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

References are listed on pages 19-24 of the specification. If Applicant wants these references considered, the references must be filed in a proper information disclosure statement.

Sequence Compliance

4. The nucleotide sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825.

37 CFR 1.821(d) states: "[w]here the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description of claims, even if the sequence is also embedded in the text or the description or claims of the patent application.

Sequences are disclosed on pages 8 and 12 of the specification that do not have SEQ ID NOS corresponding to a Sequence Listing or Computer Readable Format of the Sequence Listing.

Appropriate correction is required.

The absence of proper sequence listing did not preclude the examination on the merits however, **for a complete response to this office action, applicant must submit the required material for sequence compliance.**

Claim Objections

5. Claim 1 is objected to because of the following informalities: Claims recite "Cx40". The specification discloses this as an abbreviation for connexin 40. For clarity, it would be more appropriate to spell out connexin followed by introducing the abbreviation in parentheses (e.g.-connexin 40 (Cx40)) in claim 1. Appropriate correction is required.

Claim 1 is also objected to for its use of the term, "locus". Locus is an "address" on a chromosome and is a region of DNA. It is not synonymous with "gene" and is improperly used in the instant claim.

Claim 7 is objected to because of the following informalities: The claim recites, "as cardiac conduction system model". It has been assumed that this is a typographic error and has been interpreted as reciting, "as a cardiac conduction system model". Appropriate correction is required.

Claim 7 is also objected to because it fails to narrow the scope of that claimed in either of claims 1 or 4. An intended use or statement of what the product is useful for fails to distinguish two products.

Claim 9 is also objected to because it fails to narrow the scope of that claimed in either of claims 1 or 4. An intended use or statement of what the product is useful for fails to distinguish two products.

Double Patenting

6. Applicant is advised that should claim 1 or 4 be found allowable, claim 7 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). The "useful as" phrase fails to limit the scope of what is being claimed.

7. Applicant is advised that should claim 1 or 4 be found allowable, claim 9 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). The "wherein..." phrase fails to change the scope of what is being claimed.

Claim Rejections - 35 USC § 112, 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Scope of Enablement

8. Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A transgenic mouse whose genome comprises a reporter gene inserted into the connexin 40 (Cx40) gene such that the reporter gene is in operable linkage with the endogenous Cx40 promoter and the Cx40 gene leading to co-expression and co-localization of the reporter protein and a functional Cx40 protein and wherein said reporter gene is expressed in the atrio-ventricular node (AVN), His bundle, bundle branches, and Purkinje fibers of the cardiac conduction system (CCS)
And being enabled for:
said transgenic mouse wherein the mouse is homozygous for said reporter gene; and said transgenic mouse wherein an electrical activity of the CCS does not significantly differ from a non-transgenic control mouse and the expression profiles of the fluorescence protein in the left and right bundle branches correspond with the left and right electrical activity maps providing an image of the mouse ventricular conduction system,

does not reasonably provide enablement for:
A transgenic mouse comprising 1) any reporter gene encoding a non-fluorescent gene product 2) with any or no promoter wherein said reporter gene is incorporated into 3)

any location within the locus in which the cx40 gene is found, wherein the reporter gene is expressed in 4) any component of the CCS, wherein 5) offspring of the transgenic mouse are produced with a double eGFP positive allele, and wherein one allele is inactivated.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue".

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge

pertinent to an art at the time of invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The specification provides a means of producing a transgenic mouse with a targeted insertion of an eGFP reporter gene into the Cx40 gene (example 1, p 11-12). The targeting vector introduces, by homologous recombination, an eGFP coding sequence at the start codon of the Cx40 gene to allow for the expression of the eGFP and Cx40 driven by the Cx40 promoter (p. 7, [0030]). The specification discloses co-expression of the GFP and Cx40 in the AVN, His Bundles, bundle branches, and Perkinje fibers of the transgenic heart (p. 9-10). The specification also taught that the electrical activity of the CCS does not significantly differ from a non-transgenic control mouse and the expression profiles of the fluorescence protein in the left and right bundle branches correspond with the left and right electrical activity maps providing an image of the mouse ventricular conduction system (p.14-17).

However, the specification did not teach the invention as it is broadly claimed.

1) The claims are drawn in its greatest breadth to the use of any reporter gene protein, including non-fluorescent reporters. However, the specification only teaches the use of an eGFP and speculates about the use of other fluorescent protein-encoding genes. The specification describes the use of the transgenic mouse for in vivo and ex vivo electrical mapping of the cardiac conduction system. However, not all reporter gene, such as LacZ, will allow for the simultaneous measurement of the reporter gene in vivo and ex vivo as intended by the instant invention. Some reporter genes and their

products require the sacrifice of the mouse before the expression of the reporter gene expression can be visualized, therefore making them ineffective for in vivo or ex vivo analysis of the reporter gene and it product. Therefore, at the very least, the invention must utilize a reporter gene that can be measured in vivo or ex vivo and the only reporter gene of record capable of in vivo visualization is a fluorescent reporter. Therefore, the invention is only enabled for a fluorescence protein reporter gene.

2) The claims encompass integration of a reporter gene anywhere within the "locus of the Cx40 gene". Thus, the instant invention encompasses the integration of a reporter gene into the genome such that it is not operably linked to a promoter. For a protein to be expressed, it minimally needs to operably linked to a promoter, either of its own in a transgene construct or another promoter of strategically close by. Therefore, an artisan would not know how to express the reporter protein without the reporter gene being operably linked to a promoter. The specification teaches that the reporter gene is inserted at the start codon of the Cx40 gene as to allow it to utilize the Cx40 promoter. Furthermore, the claims require that the reporter gene be co-localized and co-expressed with the Cx40 gene. The only means the specification teaches for this and the best means of accomplishing co-expression and co-localization is by sharing the same promoter. Therefore, the specification only enables the reporter gene operably linked to the endogenous Cx40 promoter.

3) The breadth of the claims encompass inserting the reporter gene into any location in the locus of the Cx40 gene. This would encompass inserting the reporter gene into the Cx40 gene and knocking out its function. However, the specification and

the claims intend that the transgenic mouse co-express and co-localize the reporter gene and Cx40. Therefore, an artisan would not know how to co-express the reporter gene and Cx40 is the reporter gene disrupts Cx40 expression as is encompassed by the breadth of the claims. Therefore, the specification only enables an insertion that does not interfere with Cx40 gene function.

The breadth also encompasses insertion into other location within the Cx40 locus. However, insertion into other locations of the Cx40 loci will not necessarily result in the same co-expression with the Cx40 loci as is encompassed by the claims and the disclosed invention of the specification. Therefore, to assure the co-expression and co-localization of the reporter gene and Cx40, the specification only enabled that the reporter gene be inserted into the star codon of the Cx40 coding sequence.

4) The breadth of the claims encompass expressing the reporter gene in any component of the cardiac conductive system. However, the specification teaches that the sinal artrial node (SAN) does not express the reporter gene in the transgenic mouse of the disclosed invention and the SAN would be considered part of the cardiac conduction system. Therefore, the specification suggests that the reporter gene is not expressed in all components of the cardiac conduction system as is encompassed by the claims. Therefore, the specification only enables expression of the reporter gene in the AVN, His Bundles, branch bundles and Perkinje fibers where the specification demonstrated there was expression of the reporter gene and not all components of the conduction system as encompassed by the claims.

5) The breadth of the claims encompass transgenic offspring with a double eGFP positive allele (claim 5) . The breadth of this encompasses a transgenic mouse that receive two tandem copies of the reporter construct or an extra copy of the construct inserted randomly inserted. If either of these cases occurred, the expression pattern of the reporter gene would be different from that that disclosed in the specification or encompassed by the claims. Therefore, the specification does not enable double eGFP positive allele other than the a mouse that is homozygous for the targeted insert of the reporter gene.

The claims also encompass wherein one allele is inactivated (claim 6). However, the specification does not teach a situation wherein one allele is inactivated. It only teaches a mouse hemizygous for the reporter gene. Therefore, an artisan would not know how to make the instantly claimed offspring with an inactivated allele.

Furthermore, it is not clear what allele is to be inactivated as claimed. Is the a allele referring to one of the double alleles or some other allele. Therefore, since the specification does not teach the inactivation of any alleles an artisan would not know what allele is to be inactivated.

Overall, because the specification does not teach the great breadth of the invention or does not overcome the unpredictabilities described in the art, the instant invention is only enabled for a transgenic C57B1/6 x 129 mouse comprising a targeting insertion into its genome comprising a fluorescence protein reporter gene inserted in fame at a 40 gene start codon and is operably linked to the Cx40 promoter wherein said reporter gene is co-expressed and it protein is co-localized with Cx40 and wherein said

reporter gene is expressed in the AVN, His bundle, bundle branches, and Purkinje fibers of the CCS, said transgenic mouse wherein the mouse is homozygous for said targeted insertion, said transgenic mouse wherein an electrical activity of the CCS does not significantly differ from a non-transgenic control mouse and the expression profiles of the fluorescence protein in the left and right bundle branches correspond with the left and right electrical activity maps providing an image of the mouse ventricular conduction system.

Claim Rejections - 35 USC § 112, 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 2-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 recites the limitation "the knock-in reporter gene" in 2. There is insufficient antecedent basis for this limitation in the claim.

Claims 2-9 recite "a.....mouse according to". The metes and bounds of this recitation are indefinite because it is unclear if this is referring to the mouse of a previous claim or a variant of the mouse of a previous claim.

Claim 4 recites the limitation "the Cxn protein" in 2. There is insufficient antecedent basis for this limitation in the claim. Claims 5-9 depend upon claim 4.

Claims 5 recites "a double eGFP+ allele". The metes and bounds of this recitation are indefinite because it is unclear if this is mean to refer to a mouse homozygous for eGFP or to have two copies present in the same allele. Claim 6, 8, and 9 depend from claim 5.

Claim 6 recites "at least one allele which is inactivated". The metes and bounds of this recitation are indefinite because it is not clear if this recitation is referring to one or both of the double alleles or some completely different allele. Claims 8 and 9 depend from claim 6.

Claim 8 recites the limitations, "the eGFP+ cells" in line 2 and "the anatomical description" in line 3. There is insufficient antecedent basis for these limitations in the claim. Furthermore, the metes and bounds of "the anatomical description" are indefinite because it is unclear if this is referring to the anatomical structure that had cells positive for eGFP or another anatomical description. Claims 9 depends from claim 8.

Claim 9 recites the limitations, "the GFP images" in lines 1-2 and "the electrical activation maps" in line 3. There is insufficient antecedent basis for this limitation in the claim.

10. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcia S. Noble whose telephone number is (571) 272-5545. The examiner can normally be reached on M-F 9 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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